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APPEAL BRIEF Mail Stop Appeal Brief Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Attorney Docket No.	10050560-1
	Confirmation No.	4057
	First Named Inventor	WYRICK, JOHN
	Application Number	10/032,281
	Filing Date	December 21, 2001
	Group Art Unit	1637
	Examiner Name	Fredman, Jeffrey Norman
	Title: "GENOME WIDE LOCATION AND FUNCTION OF DNA BINDING PROTEINS"	

Sir:

This Brief is filed in support of the Applicant's appeal of the rejections set forth in the Office Action dated June 8, 2007. A Notice of Appeal was filed on September 10, 2007. As such this Appeal Brief is timely filed.

The Board of Patent Appeals and Interferences has jurisdiction over this appeal pursuant to 35 U.S.C. § 134(a).

The Commissioner is hereby authorized to charge deposit account number 50-1078, reference no. 10050560-1 to cover any fee required under 37 C.F.R. § 1.17(c) for filing the Applicant's brief. Additionally, in the event that the fee transmittal or other papers are separated from this document and/or other fees or relief are required, the Applicant petitions for such relief, including extensions of time, and authorize the Commissioner to charge any fees under 37 C.F.R. §§ 1.16, 1.17 and 1.21 which may be required by this paper, or to credit any overpayment, to the above disclosed deposit account.

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REAL PARTY IN INTEREST

The real party in interest in this appeal is Agilent Technologies, Inc.

RELATED APPEALS AND INTERFERENCES

There are currently no other appeals or interferences known to the Appellant, the undersigned Appellant's representative, or the assignee to whom the inventor assigned his rights in the instant case, which would directly affect or be directly affected by, or have a bearing on the Board's decision in the instant appeal.

STATUS OF CLAIMS

Claims 1-6, 8, 15-17, 87-88 and 90-92 are pending and are appealed herein.

Claims 7, 9-14, 18-86 and 89 were cancelled during prosecution.

STATUS OF AMENDMENTS

No amendments have been made subsequent to the final Office Action. All amendments have been entered.

SUMMARY OF CLAIMED SUBJECT MATTER

The rejected claims relate to a method of sample analysis. In one illustrative embodiment, the method requires cross-linking genomic DNA to DNA-binding proteins, fragmenting the cross-linked genomic DNA, immunoprecipitating a fragment of DNA using an antibody to a DNA-binding protein, and hybridizing the immunoprecipitated fragment of DNA to a microarray in order to identify the sequence of the immunoprecipitated fragment. The method may be used, for example, to identify the promoters to which a transcription factor binds.

The rejected claims require that the immunoprecipitated DNA fragment is labeled in a particular way. The claim recited labeling method requires the following steps: i. blunting the DNA fragment to produce blunt ends; ii. ligating adaptors to the blunt ends; and iii. amplifying the DNA fragment using a primer that binds to the adaptors. The DNA fragment may be labeled either during or after amplification to produce a labeled DNA fragment.

A description of claim 1, the only independent claim in this case, follows below.

Claim 1 is directed to method of identifying a region of a genome of a cell to which a protein of interest binds (page 2, lines 26-27), and requires the steps of:

a) crosslinking DNA binding protein in the cell to genomic DNA of the cell, thereby producing DNA binding protein crosslinked to genomic DNA (page 3, lines 9 and 10);

b) generating DNA fragments of the genomic DNA crosslinked to DNA binding protein in a) (page 3, lines 25-26) by sonication (page 16, line 26), thereby producing a mixture comprising DNA fragments to which DNA binding protein is bound;

c) removing a DNA fragment to which the protein of interest is bound from a first portion of the mixture produced in b) (page 3, lines 25-27);

d) separating the DNA fragment of c) from the protein of interest (page 3, lines 29-page 4, line 2);

e) labeling the DNA fragment of d) with a first fluorescent label (page 15, lines 16-18) by:

i. blunting said DNA fragment to produce blunt ends (page 70, line 18 to page 71, line 13; Fig. 1);

ii. ligating adaptors to said blunt ends (page 73, line 1; Fig. 1);

iii. amplifying said DNA fragment using a primer that binds to said adaptors (page 74, lines 1 to 12; Fig. 1); and

iv. labeling said DNA fragment either during or after said amplifying to produce a labeled DNA fragment (page 15, lines 16-18 and page 74, lines 1-12);

f) labeling a second portion of the mixture produced in b) with a second fluorescent label (page 63, lines 11-16; page 18, lines 1-5) by:

i. blunting said second portion to produce a blunted sample (page 70, line 18 to page 71, line 13; Fig. 1);

ii. ligating adaptors to said blunted sample (page 73, line 1; Fig. 1);

iii. amplifying said blunted sample using a primer that binds to said adaptors (page 74, lines 1 to 12; Fig. 1); and

iv. labeling said blunted sample either during or after said amplifying to produce a second sample (page 15, lines 16-18 and page 74, lines 1-12);

g) combining the labeled DNA fragment of e) and the second sample of f) with a DNA microarray comprising sequences that detect intergenic regions, under conditions in which nucleic acid hybridization occurs (page 18, lines 1-5); and

h) comparing results obtained from said first fluorescent label to results obtained from said second fluorescent label to identify a sequence of g) to which the DNA fragment hybridizes (page 63, lines 17-23),

whereby the sequence identified in h) indicates the region of the genome in the cell to which the protein of interest binds (page 3, lines 6-7).

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

I. The Appellants request review of the grounds for the rejection of Claims 1-6, 8, 15-17, 87, 88, 90 and 90 under 35 U.S.C. § 103(a) as being unpatentable over Strutt (EMBO J. 1997 16: 3621-3631) in view of Schena (Tibtech 1998 16: 301-306).

ARGUMENT

Claims 1-6, 8, 15-17, 87, 88, 90 and 90 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Strutt (EMBO J. 1997 16: 3621-3631) in view of Schena (Tibtech 1998 16: 301-306). As best understood by the Appellants, the Examiner believes that Strutt's chromatin immunoprecipitation method, in combination with Schena's microarray methods, renders the claims obvious.

The following arguments are directed to all claims. For the purposes of this appeal, all claims stand or fall together. Claim 1 is representative.

The rejected claims recite a particular labeling method that requires, as a separate step, blunting an immunoprecipitated DNA fragment prior to ligation of adaptors and subsequent amplification. Claim 1 explicitly recites the following step: "blunting said DNA fragment to produce blunt ends". In context, the rejected claims require that an immunoprecipitated DNA fragment is labeled by the following method:

"i. *blunting said DNA fragment to produce blunt ends*;

ii. ligating adaptors to said blunt ends;

iii. amplifying said DNA fragment using a primer that binds to said adaptors; and

iv. labeling said DNA fragment either during or after said amplifying to produce a labeled DNA fragment." (italics added by Appellants).

Because the claim recites "blunting said DNA fragment", the claim requires that a DNA fragment is made and then blunted. It is clear from the language of the claim that the so-called "blunting step", is practiced as a separate step *after* (rather than during) DNA fragmentation.

Strutt is relied upon by the Examiner to provide the above-described labeling method.

However, such a labeling method is neither taught nor suggested by Strutt because Strutt does not blunt the ends of a DNA fragment prior to ligation. Rather, according to the last four lines of col. 1 of page 3622[1] and the last paragraph of col. 2 of page 3630[2] of Strutt's disclosure, Strutt's method is one in which the adaptors are ligated directly to DNA fragments immediately after those fragments are made. At no point does Strutt mention *blunting* DNA fragments prior to adaptor ligation, as required by the rejected claims.

While not expressly articulated in the Advisory Action of August 9, 2007, it is understood from the language used in the Advisory Action that the Examiner thinks that the above-described "blunting step" must be inherently performed as part of Strutt's method.[3] This argument appears to be based on the observation that Strutt ligates blunt ended linkers onto DNA fragments.

A close review of Strutt's disclosure, however, reveals that Strutt's blunt-end linkers

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[1] "In this report, blunt-end linkers are ligated *directly* to the immunoprecipitated DNA fragments" Strutt, page 3622, col. 1, last four lines. Emphasis added by Applicants.

[2] "Cross-linking ….. and immunoprecipitation from cross-linked chromatin were carried out exactly as previously described (Orlando and Paro, 1993; Orlando *et al*, 1997), except for a modification in the PCR amplification protocol, in which a blunt-ended linker was ligated *directly* to the sonicated, immunoprecipated DNA." Strutt, page 3630, last paragraph of col. 2. Emphasis added.

[3] In the Advisory Action, the Examiner states: "In fact, Strutt necessarily makes blunt ends because Strutt ligates blunt end linkers to the DNA fragments". Given that Strutt does not explicitly teach any step in which DNA fragments are blunted, the Appellants interpret the Examiner's statement to mean that Strutt's method inherently includes a step by which DNA fragments are blunted.

are "ligated *directly*" (see footnotes 1 and 2, below) onto the DNA fragments, indicating that the DNA fragments were not blunted prior to their ligation. As such, it is clear to the Appellants that Strutt ligated adaptors onto a DNA fragment without any blunting of the DNA fragment. Strutt *did not* blunt any fragments prior to ligation.

At best Strutt may have made some DNA fragments having blunt ends during a prior step in Strutt's method, i.e., during the "fragmenting" step. However Strutt does not disclose a separate step in which the DNA fragments are blunted, as required by the rejected claims. Nor does Strutt teach that his fragmenting step results in any blunt ended fragments. At best, Strutt produces some blunt ended fragments during fragmentation, and those fragments may be directly ligated onto adaptors. Thus, Strutt's labeling method is not the labeling method recited in the rejected claims because the claims specifically call out that the blunting step occurs as a separate step *after* (rather than during) DNA fragmentation. Further, Strutt's labeling method without a separate blunting step would produce a population which might have random blunt ended fragments, but would not produce a population with uniformly blunt ended fragments, and thus would result in a different product from that resulting from the claimed method.

In view of the foregoing discussion, the Appellants submit that the Examiner has erred in that he has either mis-read Strutt as teaching an element of the rejected claims, or mis-read the claims to read on Strutt's method. Either way, a *prima facie* case of obviousness has not been established, and this rejection should be withdrawn.

With the above in mind, the Applicants also submit to the Board that the amplification method recited in the claims provides unexpected results in that the method provides unexpectedly reproducible amplification of an entire genome (see, e.g., page 18, lines 17-21, page 82, middle paragraph, and Fig. 5B, which shows that when genomic DNA is amplified is using the claim recited method and hybridized to an array of probes, 99.8% of probes on the array produced signals that were essentially identical within the error range).

The success of the claim-recited amplification method was quite unexpected and could not have been predicted by the prior art.

While the Applicants believe that a declaration should be unnecessary given that a *prima facie* case of obviousness has not been established, the Applicants submitted a Declaration under 37 C.F.R. § 1.132 by Dr. John Wyrick (the "Wyrick declaration"), the first

named inventor in this application. In his declaration, Dr. Wyrick confirms that success of the claim-recited amplification method was quite unexpected.

Since, as established above, Strutt's labeling method is different to the one recited in the rejected claims, the Applicants submit that the Examiner's main lines of reasoning for giving no weight to the Wyrick Declaration, namely that the claim-recited labeling method is the "precise labeling method performed by Strutt" and "Strutt performed the method prior to Dr. Wyrick and obtained the same result which Dr. Strutt had expected", are unsupported. Thus, Dr. Wyrick's declaration carries full weight, and should not be ignored.

In view of the foregoing discussion, the Appellants submit that the Examiner has erred in that he has given no weight to the Wyrick Declaration. Given that the claims recite a labeling method that is different to that of Strutt, the Wyrick Declaration should be given full weight.

Finally, as the Board no doubt knows, under the case law and its own rules of practice, the Office is required to consider the factual evidence in the record, including the Wyrick Declaration and its factual underpinnings, and either accept them as true or rebut them with a factual showing of its own. *In re Alton*, 76 F.3d 1168, 1175, 37 U.S.P.Q.2d (BNA) 1578, 1583 (Fed. Cir. 1996). In this case, the Examiner has provided no rebuttal of either the findings or the conclusion presented by Dr. Wyrick in his declaration. As such, the Appellants believe that the Examiner has erred for another reason.

In view of the foregoing discussion, the Applicants submit that the Examiner has made many errors, and that this rejection should be reversed.

SUMMARY

I. Claims 1-6, 8, 15-17, 87, 88, 90 and 90 are patentable over Strutt (EMBO J. 1997 16: 3621-3631) in view of Schena (Tibtech 1998 16: 301-306).

RELIEF REQUESTED

The Appellants respectfully request that all rejections of Claims 1-64 be reversed and that the application be remanded to the Examiner with instructions to issue a Notice of Allowance.

Respectfully submitted,

Date: October 31, 2007 By: /James S. Keddie, Reg. No. 48,920/

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CLAIMS APPENDIX

1. A method of identifying a region of a genome of a cell to which a protein of interest binds, comprising the steps of:

a) crosslinking DNA binding protein in the cell to genomic DNA of the cell, thereby producing DNA binding protein crosslinked to genomic DNA;

b) generating DNA fragments of the genomic DNA crosslinked to DNA binding protein in a) by sonication, thereby producing a mixture comprising DNA fragments to which DNA binding protein is bound;

c) removing a DNA fragment to which the protein of interest is bound from a first portion of the mixture produced in b);

d) separating the DNA fragment of c) from the protein of interest;

e) labeling the DNA fragment of d) with a first fluorescent label by:

i. blunting said DNA fragment to produce blunt ends;

ii. ligating adaptors to said blunt ends;

iii. amplifying said DNA fragment using a primer that binds to said adaptors; and

iv. labeling said DNA fragment either during or after said amplifying to produce a labeled DNA fragment;

f) labeling a second portion of the mixture produced in b) with a second fluorescent label by:

i. blunting said second portion to produce a blunted sample;

ii. ligating adaptors to said blunted sample;

iii. amplifying said blunted sample using a primer that binds to said adaptors; and

iv. labeling said blunted sample either during or after said amplifying to produce a second sample;

g) combining the labeled DNA fragment of e) and the second sample of f) with a DNA microarray comprising sequences that detect intergenic regions, under conditions in which nucleic acid hybridization occurs; and

h) comparing results obtained from said first fluorescent label to results obtained from said second fluorescent label to identify a sequence of g) to which the DNA fragment hybridizes,

whereby the sequence identified in h) indicates the region of the genome in the cell to which the protein of interest binds.

2. The method of Claim 1 wherein the cell is a eukaryotic cell.

3. The method of Claim 1 wherein the protein of interest is selected from the group consisting of: a transcription factor and an oncogene.

4. The method of Claim 1 wherein the DNA binding protein of the cell is crosslinked to the genome of the cell using formaldehyde.

5. The method of Claim 1 wherein the DNA fragment of c) to which is bound the protein of interest is identified using an antibody which binds to the protein of interest.

6. The method of Claim 1 wherein the DNA fragment of e) is amplified using ligation-mediated polymerase chain reaction.

7. (Canceled)

8. The method of Claim 1 further comprising:

h) comparing the sequences identified in g) with a control.

9. - 14. (Canceled)

15. The method of Claim 1 wherein after the DNA fragment is separated from the protein of interest, the DNA fragment is labeled with a fluorescent dye.

16. The method of Claim 15 wherein the fluorescent dye is selected from the group consisting of: Cy5 and Cy3.

17. The method of Claim 1 wherein the DNA fragments are generated using shearing conditions.

18.-86 (Cancelled)

87. The method of Claim 1 further comprising:

(i) identifying a DNA binding site of the protein of interest in the sequence identified in (h) wherein the protein of interest is a transcription factor.

88. The method of Claim 1, wherein said sequences are across a chromosome and the chromosome is examined to determine where the protein of interest binds.

89. (Cancelled)

90. The method of Claim 1, wherein said amplifying comprises non-specifically amplifying.

91. The method according to Claim 90, wherein said non-specifically amplifying is by ligation-mediated polymerase chain reaction (LM-PCR).

92. The method according to Claim 1, wherein said array contains spots representing all of the genome of said cell.

EVIDENCE APPENDIX

The Wyrick Declaration, filed in conjunction with the Applicant's response of August 2, 2007, is submitted in this Appendix.

DECLARATION BY JOHN WYRICK Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Attorney Docket No.	10050560-1
	Confirmation No.	4057
	First Named Inventor	WYRICK, JOHN
	Application Number	10/032,281
	Filing Date	December 21, 2001
	Group Art Unit	1637
	Examiner Name	Fredman, Jeffrey Norman
	Title: "GENOME WIDE LOCATION AND FUNCTION OF DNA BINDING PROTEINS"	

I, John Wyrick, declare:

1. I am the first named inventor of the above-referenced patent application.

2. The above-referenced patent application reports the results of method in which 1 ng of genomic DNA was labeled using a method that includes:

a) sonicating the genomic DNA to produce genome fragments;

b) blunting the genome fragments;

c) ligating the fragments to adaptors; and

d) amplifying the genome fragments using a primer that binds to the adaptors.

3. Two samples were produced using the method, one labeled with Cy-3 and the other labeled with Cy-5. Both samples were hybridized to an array of probes, and signals obtained from the array were quantified. This results obtained from the method are shown in the graph of Fig. 5B, and discussed on page 18, lines 17-21 and page 82, middle paragraph.

4. The graph of Fig. 5B shows that the method provides highly reproducible amplification of the entire genome. The success of the labeling method was unexpected.

5. I, John Wyrick, hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title XVIII of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

5/15/2007
Date

John Wyrick

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RELATED PROCEEDINGS APPENDIX

As stated in the *Related Appeals and Interferences* section above, there are no other appeals or interferences known to Appellants, the undersigned Appellants' representative, or the assignee to whom the inventors assigned their rights in the instant case, which would directly affect or be directly affected by, or have a bearing on the Board's decision in the instant appeal. As such this section is left blank.